UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/670,118	06/25/96	FODOR S	16528X-00056

020350 18M2/0903
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EXAMINER	
ZITOMER, S	
ART UNIT	**PAPER NUMBER**
1807	11

DATE MAILED: 09/03/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/670,118	Applicant(s) Fodor et al.
	Examiner Stephanie Zitomer	Group Art Unit 1807

☒ Responsive to communication(s) filed on *Jun 5, 1997* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-10 and 26-39* is/are pending in the application.

Of the above, claim(s) *1-10 and 37* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *26-36, 38, and 39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3, 8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status

1. Applicant's election without traverse of Group II, claims 26-39 including newly submitted 31-39 in Paper No. 9 and the polynucleotide species is acknowledged. New claim 37 properly belongs in Group I in being drawn to a substrate as in the Group I compositions. Claims 1-10 and 37, drawn to a nonelected invention, are withdrawn from prosecution. The relationship of the new claims to those of PCT publications having US patent applications as priority documents is noted. Applicant is correct in stating that the present claims including those newly submitted have an effective filing date at least three years prior to those of the above-mentioned US patent applications. The present claims of the latter applications are not patentable over applicant's claims.

Informalities

2. The disclosure is objected to because of the following informalities:

(a) Applicant is reminded that Figures 4A-4M must be specifically referred to in the specification at "Brief Description of the Figures".

(b) Applicant is reminded that the abstract must be on a separate sheet and must not contain other text.

© Applicant is reminded that a substitute specification is required containing the amendments set forth in the Preliminary Amendment filed June 25, 1996 which are so numerous as to constitute confusion for the printer when the application goes to issue.

Appropriate correction is required.

New matter

3. Claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not describe the kit or any combination of array on a solid support and references nucleic acids in a container or even the array and reference nucleic acid without a container. The passages cited by applicant in support of the claims, in fact, do not. In addition to enablement the first

paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. Clearly, the present specification does not provide a written description of the claimed kit.

Rejections under 112, first and second paragraphs

4. Claims 26-36, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being believably enabling for a method and kit for identifying nucleic acid sequence differences employing a substrate having multiple oligonucleotide probes attached at a density of some 2500 probes per square centimeter based on the prior art of Southern (WO 89/10977), does not reasonably provide enablement for said method and kit employing substrates having probes attached thereto at a density of "at least 10,000 probes per square cm". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention method and kit employing a substrate having a probe density commensurate in scope with these claims. The specification discusses the number of different-nucleotide sequence probes required to obtain the complete set of permutations for the four nucleotides A, T, G, C for a number of different-length probes on a substrate (pages 34, 35, 37); the projected sizes of substrate regions to which the probes may be attached (page 36); and complications in performing the claimed invention assays arising from the relationship between the length o f the target sequence and the length of the probe (pages 29-32). However, the specification does not describe how to perform the claimed invention assay in which the probe density on the substrate is "at least 10,000 probes per square centimeter" or, in other embodiments, "at least 100,000 per square centimeter" and "at least 1,000,000 per square centimeter". In the first place, the formation of a substrate bearing "probes" is not described as the eight trimers in the example at page 108 are too short to act as probes in a sequencing-by-hybridization reaction and eight cannot be considered exemplary of an array of "at least" 10,000 to a million probes in a square centimeter. Secondly, the specification is absent any demonstration of the "identifying" method of the claimed

invention. There is no example of measurement of a number of multiple oligonucleotide probes attached to a substrate, only the putative measurement of the number of free amino groups on the derivatized substrate as a function of fluorescein labeling (page 117, lines 11-15). In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. In a research news article in Science dated September 27, 1991 inventor Fodor is quoted, "We have just completed moving up to 65,000 sites in a 1.28-cm-square array" which is a density of approximately 50,781 per square centimeter. It is noted that this is sites only, not probes, and a long way from use in a nucleic acid assay. Clearly, the claims of methods and kit for identifying nucleotide differences using an array of "at least" 10,000 to a million probes per square centimeter or more was neither described nor enabled as of the filing date of the application.

5. Claims 26-36, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 26-31 are indefinite in lacking proper antecedent basis in step (b) "exposing" for "oligonucleotide probes [that] have hybridized" in steps © and (d) because "exposing" does not mean or imply "hybridizing".

(b) Claims 32-34 are indefinite at (b)(ii) because it appears that the "second labelled nucleic acid" should be a "second collection of labelled nucleic acids" consistent with the preamble; i.e., "second labelled nucleic acid" lacks proper antecedent basis in the preamble.

© Claims 32-34 are indefinite at © in the recitation "the binding" which lacks proper antecedent basis in the previous steps of "providing" and "contacting", neither of which reads as "binding" or causing "binding".

(d) Claims 32-34 are indefinite in the recitation "binding" as it is unclear whether this intends "hybridization" or some other interaction. For example, in claim 35 nucleic acids are "bound" to a support.

(e) Claims 35 and 36 are indefinite in the recitations "array" and "at least two members" because the number of target nucleic acids is indeterminate in lacking an upper limit.

(f) Claims 38 and 39 are indefinite because the recitation "predominantly" is a quantity-designating term whereas no criteria are recited for determining its represented quantity. It is suggested that the term does not contribute meaning to the claim and can be deleted.

(g) Claims 38 and 39 are indefinite in lacking proper antecedent basis for the fluorescent nucleic acids in the "examining" step. It is suggested to amend these nucleic acids to recite "labeled nucleic acids".

(h) Claim 39 is indefinite in the recitations "polypeptide biopolymers" and "biopolymer" in lines 2 and 3 which lack proper antecedent basis in claim 38.

Rejections over the prior art

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern (WO 89/10977) in view of the patent to Fodor et al. (5,445,934) (the Affymax patent). Southern discloses a method for identifying nucleotide differences between the

sequence of a target nucleic acid and the sequence of a reference nucleic acid comprising hybridizing the target nucleic acid with an array of about 1000 different oligonucleotide probes of known sequence at known locations on a substrate wherein the nucleic acid is labelled, e.g., with a fluorescent label and using a computer to analyze the sequence differences (page 4, line 23-page 5, line 10; page 14, lines 13-16 and 26-29). The claimed invention method differs from that of Southern in the method of making the array (claim 27) and the density of the probes in the array: "at least 10,000" to "at least 1,000,000" in a square centimeter (claims 26, 30, 31). However, the Affymax patent teaches a nucleic acid array on a substrate (columns 31-32, claims 1-10) and method of making it which is that recited in present claim 27 (column 3, lines 8-32) wherein the substrate is stated to support more than 1000 to more than 100 million polymers in a square centimeter (column 15, lines 48-61). The patent substrate is useful for determining sequences that bind to a receptor wherein the receptors are labeled, e.g., with a fluorescent label (column 3, lines 45-53) and can be used "to establish DNA or RNA binding sequences" (column 7, lines 20-23). It would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the Southern method of identifying nucleic acid sequence differences with the teachings of the Affymax patent to obtain the claimed invention because the skilled artisan would have been motivated to increase the probe density by Southern's statement that "More efficient methods for analyzing complex sequences are needed to bring the full power of molecular genetics to bear on the many biological problems for which there is no direct access to the gene or genes involved" (page 5, paragraph "4") in obvious reference to the exigencies of the Human Genome Project.

7. Claims 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern (WO 89/10977) in view of Fodor et al. (5,445,934) for the reasons stated above and further in view of Bahl et al. (5,215,882) and Fung et al. (4,855,225). Southern additionally discloses a method for comparing nucleic acid sequences in two or more collections of nucleic acid molecules, e.g., the mRNA from two different cell types, comprising hybridizing the two collections to an array of target oligonucleotides bound to a solid surface (columns 31-32, claims 1-10) and detecting hybridization of nucleic acids of

the first and second collections (page 6, lines 6-13). The Affymax patent additionally teaches that the support can be beads (column 7, lines 59-61). The claimed invention method differs from that of Southern in view of the Affymax patent in the requirement for "first and second labels [are] distinguishable from each other". However, Bahl et al. teach a hybridization assay in which an array of two different nucleic acid sequences is bound to a solid support and the two sequences are detected in the same hybridization assay "by using appropriately labelled probes" (column 5, lines 23-39) which is interpreted as differentially labelled probes as were known in the art and taught by Fung et al. (column 12, lines 11-13). Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Southern in view of the Affymax patent for identifying nucleic acid sequence differences with the teachings of Bahl et al. and Fung et al. to obtain the claimed invention because the skilled artisan would have been motivated to combine the hybridization steps using differentiable probes for the expected benefit of saving time and labor. This rejection can be overcome by amending claim 32 to recite that the first and second nucleic acid collections are hybridized simultaneously to the target nucleic acids. Hybridization of different probes appears to be done in separate steps in Southern and in Bahl et al. and claims 32-34 in their present form are interpreted to require separate hybridization steps.

8. Claims 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Affymax patent (as above) in view of Perkin Elmer Cetus (kit insert, Oct. 1988) and further in view of Fung et al. (4,855,225). The Affymax patent discloses a solid support having an array of target nucleic acids bound thereto wherein the array has at least two members (column 8, lines 22-29). The patent array is used for determining sequences that bind to a receptor wherein the receptors are labeled, e.g., with a fluorescent label (column 3, lines 45-53) and can be used "to establish DNA or RNA binding sequences" (column 7, lines 20-23). The claimed invention nucleic acid array differs from that of the Affymax patent in being provided in a kit. However, Perkin Elmer Cetus teach that nucleic acids and other reagents for DNA sequencing are available in a commercial kit. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was

made to modify the nucleic acid array of the Affymax patent with the teachings of Perkin Elmer Cetus to obtain the claimed invention because the skilled practitioner in the art would have been motivated to provide a kit for the expected benefit thereof in commercial applications. Absent unexpected results or evidence to the contrary it would have been obvious and/or known to the skilled practitioner to include multiple fluorescent labels in a kit containing multiple target nucleic acids.

9. Claims 38 and 39 are free of the prior art. The recitation "mixture of labeled nucleic acids" distinguishes the claimed invention over Southern because neither this reference not other prior art of record contemplates or suggests simultaneous hybridization of mixed nucleic acids.

Obviousness-type double patenting

10. Claims 26-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. patent no. 5,445,934 in view of Southern and further in view of the Affymax patent, both references described above. Southern discloses a method for identifying nucleotide differences between the sequence of a target nucleic acid and the sequence of a reference nucleic acid comprising hybridizing the target nucleic acid with an array of about 1000 different oligonucleotide probes of known sequence at known locations on a substrate wherein the nucleic acid is labelled, e.g., with a fluorescent label and using a computer to analyze the sequence differences (page 4, line 23-page 5, line 10; page 14, lines 13-16 and 26-29). The claimed invention method differs from that of Southern in the method of making the array (claim 27) and the density of the probes in the array: "at least 10,000" to "at least 1,000,000" in a square centimeter (claims 26, 30, 31). However, the Affymax patent teaches a nucleic acid array on a substrate (columns 31-32, claims 1-10) and method of making it which is that recited in present claim 27 (column 3, lines 8-32) wherein the substrate is stated to support more than 1000 to more than 100 million polymers in a square centimeter (column 15, lines 48-61). The patent substrate is useful for determining sequences that bind to a receptor wherein the receptors are labeled, e.g., with a fluorescent label (column 3, lines 45-53) and can be used "to establish DNA or RNA binding sequences" (column 7, lines 20-23). It

would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to use the substrate of the patent claims which is the same as that of the claimed invention and has a higher number of nucleic acids in the array because the skilled artisan would have been motivated to increase the probe density by Southern's statement that "More efficient methods for analyzing complex sequences are needed to bring the full power of molecular genetics to bear on the many biological problems for which there is no direct access to the gene or genes involved" (page 5, paragraph "4") in obvious reference to the exigencies of the Human Genome Project.

Conclusion

11. No claim is allowed. However, claims 32-34, 38 and 39 can be placed in condition for allowance by compliance with the suggestions and 112 requirements stated above.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Stephanie W. Zitomer, Ph.D.
August 27, 1997

STEPHANIE W. ZITOMER
PRIMARY EXAMINER
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